REMARKS

Claims 1-80 were previously cancelled. Claims 81-104 are withdrawn. Claims 107, 108, 132, 143 and 165 are canceled without prejudice, claims 105, 125, 126, 139-142, 147, 156-157, and 166 are amended, and claims 172-173 are added by the present amendment. The amended and new claims are supported throughout the application, e.g., at page 5, lines 4-5; page 7, lines 4-10 and 23-25. No new matter has been added.

Applicants reserve the right to pursue any canceled subject matter in one or more continuing applications.

Upon entry of this amendment, claims 105-106, 109-131, 133-142, 144-164 and 166-173 will be under examination.

Drawings

The Examiner states that the drawings filed with the application on August 18, 2000, have been objected to by the draftsman. Applicants note that a transmittal of formal drawings was filed on August 31, 2001. The formal drawings complied with 37 C.F.R. §§ 1.84 and 1.152. Applicants respectfully request that the formal drawings currently on file be accepted.

Specification

As requested by the Examiner, the specification has been amended to recite the generic name for terms having a trademark (™) or registered trademark (®) symbol in instances where a generic name is not already provided. No new matter is added.

Objections

Claims 165 and 166 are objected to as not further limiting the base claims. Claims 165 and 166 have been canceled, thereby obviating this objection.

Rejections Under 35 U.S.C. §112, First Paragraph

Written Description

Claims 139-142 and 152-169 are rejected as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Examiner states that "'a substance which prevents the removal of at least one mannose residue distal to pentasaccharide core of a precursor oligosaccharide of GCB' other than class 1 and 2 mannosidase inhibitors lacks sufficient written description needed to practice the invention of claims 139-142 and 152-169." This rejection has been overcome by amending claim to recite contacting the cell with a class 1 mannosidase inhibitor. The Examiner has acknowledged written description support for this limitation. The narrowing amendment is made without prejudice. Applicants reserve the right to pursue the canceled subject matter in one or more continuing applications.

Enablement

Claims 105, 106, 109-132, 137 and 138 are rejected for lack of enablement. The Examiner provides the following grounds for the rejection:

> the specification, while being enabled for a human cell comprising a human GCB remodeled to contain terminal mannose residues using mannosidase inhibitors and knockout cells for human mannosidases, does not reasonably provide enablement for a cell that is not capable of expressing a human GCB comprising a precursor oligosaccharide and for a cell that while capable of expressing a human GCB comprising a precursor oligosaccharide is not affected by kifunensine or a knockout non-human cell for mannosidase of unknown structure.

This rejection has been met, in part, and is traversed, in part. Claims 125 and 126, which cover mannosidase knockout and antisense cells, have been limited to human cells, thereby obviating their rejection. Claim 105 has been substantially narrowed to recite a mammalian cell. The rejection, insofar as it relates to the present claims, is respectfully traversed. Because the N-terminal glycosylation machinery is similar in all mammalian cells, a skilled artisan would understand and could reasonably predict that human GCB would be processed similarly in any mammalian cell in which it was expressed.

The claimed methods can work with any mammalian cell expressing a human GCB. Human GCB has several potential N-linked glycosylation sites. The N-linked glycosylation machinery of mammalian cells can act on human GCB to produce GCB containing complex glycans. (Other types of cells, e.g., insect cells, do not typically synthesize complex glycan

structures on glycoproteins.) As discussed in the specification, e.g., in the paragraphs bridging pages 27 and 28, and at page 30, line 26, to page 32, line 25 (and as detailed in the response filed on October 18, 2002), N-linked oligosaccharide processing of the precursor oligosaccharide $Glc_3Man_9GlcNAc_2$ of GCB occurs in 3 steps: (1) removal of the 3 glucose (Glc_3) residues from the precursor oligosaccharide, (2) removal of mannose residues by mannosidase I and mannosidase II, resulting in GCB containing $Man_3GlcNAc_2$, and (3) addition of various sugar residues, including complex sugars, to the resulting trimmed core. This process results in unmodified mature human GCB having 3 mannoses in the pentasaccharide core, internal to complex sugars that are added to the molecule during the third stage of processing. Thus, human GCB expressed in a mammalian cell includes complex oligosaccharide chains. The presently claimed methods can be used to modify human GCB expressed in mammalian cells to contain fewer complex, and more high mannose, glycan chains. As detailed below, it is known in the art that GCB is processed via the three step-pathway described above, and has highly similar carbohydrate structure, when expressed in various mammalian cells including, for example, human cells, hamster cells, and porcine cells.

In one example, recombinant human GCB expressed in Chinese hamster ovary cells (CHO cells) was in use for the treatment of Gaucher's Disease at the time of filing. The recombinant, CHO-produced enzyme is processed like the native human GCB through the carbohydrate biosynthetic process described above, and results in GCB which, like the native human GCB, has primarily complex glycans. See, e.g., Friedman, Reference AQ in the IDS filed on November 27, 2000. Friedman notes at page 2809, first paragraph of *Results* section:

> Successive removal of terminal sialylic acid, galactose, and N-acetyl-glucosamine sugars from the complex carbohydrate chains of human placental-derived glucocerebrosidase (pGC) and recombinant [CHO produced, human] glucocerebrosidase (rCGC) significantly improved their abilities to compete for [binding to macrophages].

In another example, porcine cells undergo similar processing of GCB, i.e., they produce GCB having complex glycan chains as a result of the carbohydrate processing steps described above. See, e.g., Erickson, reference AO in the IDS filed on November 27, 2000. Erickson compared the biosynthesis of GCB from porcine kidney cells and human fibroblasts and found them to be very similar. As discussed in Erickson at page 14323, first column:

the carbohydrate side chains added to porcine kidney glucocerebrosidase during biosynthesis undergo conversion from endoglycosidase-H sensitive high mannose carbohydrate [processing step 2] to endoglycosidase-H resistant complex carbohydrate [processing step 3].

As can be seen by the above examples, because the N-terminal glycosylation machinery is similar in all mammalian cells, human GCB expressed in human cells and hamster cells, as well as GCB expressed in porcine cells, are processed via the same N-terminal glycosylation pathway and have highly similar resulting carbohydrate structure. A skilled artisan would understand and could reasonable predict that human GCB would be processed similarly in any mammalian cell in which it was expressed. The Examiner has provided no evidence that this is not the case. As evidenced by the recombinant, CHO produced, human GCB of the prior art (see e.g., Friedman, cited by the Examiner), it is a routine matter for one of skill in the art to express human GCB in a non-human mammalian cell. One simply transfects a mammalian cell with the known human GCB coding sequence. In addition, guidance in this respect is provided in the specification, e.g., at pages 28-30.

In another aspect of the rejection, the Examiner asserts that Applicants do not provide information about what types of cells are affected by kifunensine. The present claims have been limited to mammalian cells. Given Applicants' disclosure, there is no reason to think (and the Examiner has provided no evidence) that kifunensine would not work in mammalian cells as a class.

Therefore, given the specific limitations recited in the present claims, the high level of skill and knowledge in the art regarding N-liked glycosylation of GCB in mammalian cells and the use of mannosidase inhibitors, the detailed guidance provided by Applicants regarding same, the disclosure of working examples, and the routine nature of any experimentation that might be required to practice the claimed methods, the present claims are clearly enabled. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 105, 106 and 109-171 are rejected as allegedly indefinite. In one aspect of this rejection, the term "hmGCB" is said to be unclear. This rejection has been met by amending

claims 105 and 139 (the only independent claims) to recite that the hmGCB comprises a carbohydrate chain having at least four mannose residues. This amendment is supported, e.g., at page 5, lines 4-5, of the specification.

Claims 125 and 151 are said to be indefinite in the recitation of "at least one." This basis for the rejection is traversed. The term "at least one" is clear to a skilled artisan. It simply means one or more. However, in an effort to expedite prosecution, claims 125 and 151 have been amended to delete this language. The amendment does not change the scope of the claims.

Claim 139 is rejected because it "reads on any regulatory sequence. . .that for any reason, directly or indirectly can affect the expression of an endogenous GCB." Although Applicants disagree that the claim is unclear, in an effort to expedite prosecution, claim 139 has been amended to explicitly recite that the regulatory sequence is operably linked to the endogenous GCB coding region.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. § 103

Claims 105, 106, 109-124, 132-135, 137 and 138 are rejected as unpatentable over Friedman in view of Smith. Friedman teaches the production of recombinant GCB in CHO cells, but does not teach or suggest the use of kifunensine. Smith discloses the use of kifunensine to inhibit mannosidases in HT29 cells, but has nothing to do with GCB. The Examiner states that the motivation to combine the references *"[stems] from the importance of such preparation obtained by any available method as taught by Friedman et al."* This rejection is respectfully traversed.

To establish prima facie obviousness of a claimed invention, the prior art must provide a motivation and reasonable expectation of success to arrive at the specifically claimed methods. Such a motivation is nowhere to be found in the cited references. The Examiner has provided no evidence of a specific motivation to contact a cell expressing GCB with the specifically recited molecule, kifunensine. A showing of a suggestion, teaching, or motivation to combine "must be clear and particular...Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" In re Dembiczack, 175 F.3d 994 (Fed. Cir. 1999). The

Examiner's broad, generic basis for finding motivation is no more than a statement than the claimed methods are desirable. This is clearly insufficient to support a prima facie case of obviousness.

The fact that it may be desirable or important to produce high mannose GCB does not make any one particular method of doing so obvious. Friedman uses exoglycosidases to modify recombinantly produced GCB isolated from CHO cells. Friedman provides no more than a broad, general disclosure that "alternative" methods may work to produce carbohydrate-remodeled GCB. The only disclosure about such methods in Friedman is the following:

> In alternative embodiments, remodelling may be accomplished by utilizing mutant cell lines deficient in certain carbohydrate synthetic pathways. Other methods of remodelling include chemical modification of the oligosaccharide of the *purified* recombinant GCR (Friedman 6:12-15, emphasis added).

As can be seen by the above passage, neither of the only two methods that Friedman suggests relates to using any mannosidase inhibitor, of any class (much less kifunensine), by contacting it with a cell expressing GCB. Friedman only suggests using "chemical modification" (an extremely broad term) of purified GCB, not during synthesis in the cell. Thus, Friedman points in completely different direction than the claimed methods. Smith discloses kifunensine but has absolutely nothing to do with GCB. Even if Friedman did suggest the idea of treating a cell with chemical modifiers of carbohydrate processing (which it does not), such a disclosure would not suggest or provide a reasonable expectation of success for a skilled artisan to use any one particular chemical for doing so. The Federal Circuit has repeatedly held that the fact that a claimed species (kifunensine) is encompassed by a prior art genus (chemical carbohydrate modifiers) is not sufficient by itself to establish a prima facie case of obviousness (MPEP 2144.08).

The Examiner argues that Applicants' argument that Friedman does not suggest the claimed methods "is not persuasive because the rejection is 103 not 102 and therefore does not need to contain all elements of the invention but has to make it obvious. . . Smith et al teach the requisite remodeling of human glycoproteins without specifically mentioning GCB." However, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the specific

combination (MPEP 2143.01). The Examiner has not shown the desirability or obviousness of combining Friedman and Smith in particular. Applicants expect that the Examiner could have found dozens of references, each one disclosing a different chemical modifier of carbohydrates. Without using Applicants' disclosure and/or claims as a template, it would have been impossible for the Examiner to choose kifunensine from the large group of known carbohydrate modifiers, to combine with Friedman. Thus, the Examiner has clearly used hindsight to pick and choose the elements of the claims from the art. This is impermissible. Accordingly, a prima face case of obviousness has not been made.

Moreover, even if a prima facie case of obviousness had been made (which it clearly has not), the claimed methods have surprisingly advantageous properties. As discussed at page 53, lines 17-21, uptake of GCB from kifunensine treated cells was 14-fold over background and 73% inhibitable by mannan. Uptake of GA-GCB from untreated cells was approximately 3-fold over background and 53% inhibitable by mannan. Thus, the claimed methods provide GCB having surprisingly advantageous properties.

Accordingly, Applicants respectfully request that the rejection be withdrawn.